PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Attorney Docket No.: 2508.11US02

Salin-Nordstrom Confirmation No.: 1667

Application No.: 09/644,498 Examiner: C. Nichols

Filed: August 23, 2000 Group Art Unit: 1647

For: TRANSDIFFERENTIATION OF GLIAL CELLS

BRIEF FOR APPELLANTS

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from an Advisory Action dated August 24, 2004 in light of the Final Office Action dated May 13, 2004 wherein claims 65-89 were finally rejected. Applicants appeal the rejection of claims 65-89. Attention is also directed to the concurrently filed Notice of Appeal.

REAL PARTY IN INTEREST

Spinal Cord Society, Inc., a nonprofit corporation organized under the laws of the state of Minnesota, and having offices in Fergus Falls, MN, has acquired the entire right, title and interest in and to the invention, the application, and any and all patents to be obtained therefore.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims 65-89 stand rejected. No other claims are pending. The pending claims are listed in Appendix A.

The Advisory Action of August 24, 2004 states that all of the previous Objections and Rejections are maintained for the reasons set forth in the previous Office Action of May 13, 2004.

STATUS OF AMENDMENTS

The Amendment After Final filed on July 27, 2004 was entered, as per the Advisory Action of August 24, 2004.

SUMMARY OF INVENTION

The invention relates an in vitro method to use a population of astrocytes produce a population of cells that includes neurons and/or oligodendrocytes, e.g., see page 4, lines 1-5. Certain culturing procedures and compositions for accomplishing this invention are described.

ISSUES

1. Do claims 65 and 77 satisfy the written description requirements of 35 U.S.C. §112, first paragraph?

2. Do claims 65-89 satisfy the enablement requirements of 35 U.S.C. §112, first paragraph?

3. Are the claims 65-71, 73-83, and 85-89 novel under 35 U.S.C. §102 in light of U.S. Patent 5,753,506 to Johe?

GROUPING OF CLAIMS

1. Claims 65-89 form a single claim group directed to methods of culturing cells.

ARGUMENT

I. LEGAL BACKGROUND

The Court of Appeals for the Federal Circuit has exclusive appellate jurisdiction for cases arising under the patent law under 28 U.S.C. § 1295 (a)(1). The Federal Circuit has adopted as binding precedent all holding of its predecessor courts, the U.S. Court of Claims and the U.S. Court of Customs and Patent Appeals. South Corp. v. U.S., 215 USPQ 657 (Fed. Cir. 1982). Therefore, unless they have been overruled en banc, CCPA cases are binding precedent for the present appeal.

A. ANTICIPATION

1. Examiner's Burden

The Examiner has the burden of establishing a prima facie case of anticipation. As such, the Examiner must provide a reference that discloses every element as set forth in the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP §2131).

2. A Single Reference Must Identically Disclose Every Element Set Forth In a Claim To Anticipate The Claim

"In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound..." MPEP 2122 citing In re Schoenwald, 22 USPQ2d 1671, (Fed. Cir. 1992). "For a prior art reference to anticipate in terms of 35 U.S.C. § 102, **every element of the claimed invention must be identically shown in a single reference.**

These elements must be arranged as in the claim under review, but this is not an 'ipsissimis verbis' test." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir, 1990)(Internal citations omitted and emphasis added.).

"If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is 'inherent' in its disclosure. To establish inherency, the intrinsic evidence 'must make it clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 49 USPQ2d 1949, 1950, 1951 (Fed. Cir. 1999), citing Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

"Every element of the claimed invention must be literally present, arranged as in the claim. **The identical invention must be shown in as complete detail as is contained in the patent claim.**" Richardson v. U.S. Suzuki Motor Corp., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)(Internal citations omitted, and emphasis added.); see also MPEP 2131. "Here, as well, anticipation is **not** shown by a prior art disclosure which is only 'substantially the same' as the claimed invention." Jamesbury Corp. v. Litton Industrial Products, Inc., 225 USPQ 253, 256 (Fed. Cir. 1985)(emphasis added).

B. WRITTEN DESCRIPTION REQUIREMENT

Under 35 U.S.C. § 112, first paragraph, the "specification shall contain a written description of the invention..." It has long been held that the written description requirement is separate from other patentability requirements. In re DiLeone, 168 USPQ 592, 593 (CCPA 1971)("[I]t is possible for a specification to enable the practice of an invention as broadly as claimed, and still not describe that invention."). It has also long been held that the specification does not need to use the exact language of the claim for

the written description requirement to be satisfied. In re Smith, 178 USPQ 620, 624 (CCPA 1973)("This court has held that claimed subject matter need not be described in haec verba in the specification in order for that specification to satisfy the description requirement, although where there is exact correspondence between the claim language and original disclosure, the description requirement would normally be satisfied."). "A fairly uniform standard for determining compliance with the 'written description' requirement has been maintained throughout [the period from the Federal Circuit's inception]: 'Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" Vas-Cath, Inc. v. Muhurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)(quoting from In re Gosteli, 10, USPQ2d 1614, 1618 (Fed. Cir. 1989)).

C. ENABLEMENT REQUIREMENT

As described in MPEP 2164.04 (emphasis added), "**the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.**" In the absence of such a basis, there can be no proper enablement rejection.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. Even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The *Wands* factors are potentially relevant to determine if undue experimentation is required. MPEP 2164.01(a).

II. ANALYSIS - WRITTEN DESCRIPTION REJECTIONS

Claims 65 and 77 were rejected for a lack of written description. May 13, 2004 Office Action, ¶4. This rejection was renewed in the Advisory Action of August 24, 2004. The rejection states that the specification does not contain support for "a cell derived from a human neural progenitor cell". This rejection, however, is moot because the claims do not recite such a limitation.

Instead, the claims, as amended July 27, 2004, recite "an in vitro cell culture consisting essentially of astrocytes derived from a human neural progenitor stem cell". The Examiner has pointed out that this specific language is supported by the specification: "The Specification teaches that the cultures used in the Examples were astrocytes from human neural stem cell derived astrocytes (Example 6.1.1)". May 13, 2004 Office Action, ¶7. As the Examiner correctly pointed out, the specification of the patent, e.g., in Example 6.1.1 (particularly, page 18, lines 1-4), describes an in vitro cell culture consisting essentially of astrocytes derived from a human neural progenitor stem cell.

The Examiner's rejection is moot, the specification supports the present claims, and there are no arguments on record that are directed to rejection of this language. Therefore, there is no basis for this rejection. Withdrawal of the rejection is therefore requested.

III. ANALYSIS - ENABLEMENT REJECTIONS

Claims 65-89 were rejected for a lack of enablement. **The Examiner, however, has pointed out that the present claims *are* enabled**. Referring to the May 13, 2004 Office Action, ¶5, the Examiner stated that the specification enabled:

A method to produce a population that includes neurons and/or oligodendrocytes, the method comprising the following steps:

(a) preparing an in vitro culture consisting essentially of astrocytes derived from human neural stem cells;

(b) dissociating and plating said cell culture; and

(c) maintaining said culture in serum-free media and treated with bFGF plus heparin for at least one day,

thereby producing a population of cells that include neurons and/or oligodendrocytes.

A comparison of this claim to the present claim 65 shows that they are worded essentially identically except that "medium essentially free of serum" is claimed instead of "serum-free medium" and the medium is claimed to be "comprising bFGF" instead of "treated with bFGF plus heparin". The Examiner has not made a case for rejecting "medium essentially free of serum" or medium "comprising bFGF". Since serum-free medium is enabled, it is reasonable to assume that a person of ordinary skill in the art can make a medium that is essentially free of serum, for example by placing a drop of serum in the medium that is so minute in quantity as to have essentially no effect. And since "treated with bFGF plus heparin" is enabled, it is reasonable to believe that a person of ordinary skill can treat cells by using a medium comprising bFGF, e.g., a medium of bFGF plus heparin.

As discussed above, the Examiner has already pointed out that an in vitro culture "consisting essentially of astrocytes derived from human neural stem cells" that respond to the claimed treatment by "producing a population of cells that include neurons and/or oligodendrocytes" is enabled and supported by adequate written description. The Advisory Action makes a passing reference to a failure to differentiate the claimed astrocytes from mature and/or adult astrocytes that do not have the capacity to

transdifferentiate. Advisory Action ¶ 2. Since the present claim language was clearly supported by the Examiner in the Office Action of May 13, 2004 with regards to enablement, this statement by the Examiner is not believed to be a reversal of the Examiner's May 13, 2004 arguments in favor of the present claims.

As the Examiner has pointed out, there is support for claim 65 in the specification. For instance, page 18, lines 1-5 describes the claimed process in terms of using an "added factor". Page 18, line 7 indicates that bFGF is an added factor. Example 3, starting at paragraph numbered 8.0 on page 21, provides a working example, with: Cultured astrocytes being cultured as earlier described in, e.g., paragraph numbered 6.1.1 starting on page 18; Dissociated and plated on tissue culture plastic; The cells being cultured with 20 ng per ml bFGF plus heparin; and then placed in various media, with neurons (Fig. 3A) and oligodendrocytes (Fig. 3C) being thereby produced. Further, the claims are directed to using commonly available materials in ways that are easily practiced by ordinary artisans, and the claims are further supported by working examples. Therefore the claims are enabled.

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In the present case, there is no basis because the Examiner has gone on record as essentially agreeing that the present claims are enabled. As described above, the claims are supported by ample disclosure and can be readily practiced by ordinary artisans. And claim 77 has been amended to depend upon claim 65 so that the rejection of claim 65 is moot. In the absence of arguments showing that there is no enablement, this rejection can not stand. Withdrawal of this rejection is respectfully requested.

IV. ANALYSIS - ANTICIPATION REJECTIONS

Claims 65-71, 73-83, and 85-89 were rejected for anticipation in light of U.S. Patent No. 5,753,506 (the '506 Patent). A prima facie case of anticipation requires that the cited publication teach or suggest every claimed limitation. The present claims are directed to an "in vitro cell culture consisting essentially of astrocytes derived from a human neural stem cell". The '506 Patent does not teach or suggest this limitation. Therefore, there is no proper prima facie case of anticipation.

The paragraph numbered 29 of the May 13, 2004 Office Action suggests that the initial dissociation of cells from a brain would create a culture that comprised astrocytes. The '506 Patent, however, does not provide the element of in vitro cell culture consisting essentially of astrocytes derived from a human neural stem cell, which is presently claimed. In fact, as described below, the '506 Patent teaches away from preparing cultures of differentiated cells such as astrocytes.

The '506 Patent teaches that there are four essential steps in its culturing process to isolate and differentiate the CNS stem cells, see Columns 11 and 12. The first step is the initial dissociation of cells from tissue (Col. 11, lines 27-32). The second step is the supply of growth factor at an indicated concentration. (Col. 11, lines 50-59). The third step is passaging the cells before they reach a critical density of about 50%. (Col. 11, line 60-64). The fourth step is using trypsin when passaging the cells. (Col. 12, lines 10).

After these steps, the differentiation of the CNS stem cells is achieved by simply removing the mitogen from the medium. (Col. 12, lines 24-30). In order for effective controlled differentiation to be achieved, the cells must be in a homogenous state that can be achieved by following the four essential steps. (Col. 12, lines 27-30). The second step of supplying the growth factor is needed to suppress the differentiation of the stem cells into other cell types and to maintain this homogeneity. (Col. 11, line 53-55). All of these procedures yield a culture system for obtaining a homogenous population of the CNS stem

cells that can be differentiated into neurons, oligodendrocytes, and astrocytes. (Col. 12, lines 31-33). It is well accepted in the biological arts that a homogenous culture of stem cells is not equivalent to a culture with a large proportion of astrocytes.

The '506 Patent thus teaches that homogenous populations of CNS stem cells are to be obtained and maintained as part of a process of differentiating them into other cell types, such as *astrocytes*. In contrast, what is claimed is a process that involves using a culture consisting essentially of *astrocytes* as part of a process of developing other cell types. There is no disclosure in the '506 Patent that even vaguely suggests making a culture consisting essentially of astrocytes as part of a process of developing other cell types. In fact, the '506 Patent teaches that its processes are for obtaining a homogenous population of the CNS stem cells that can be differentiated into other cell types such as astrocytes. A person of ordinary skill in these arts would not be inclined to use astrocyte cultures after reading the '506 Patent because the '506 Patent teaches that factors are to be used to suppress differentiation to thereby maintain homogenous stem cell cultures.

The Advisory Action makes a passing reference to a failure to differentiate the claimed astrocytes from mature and/or adult astrocytes that do not have the capacity to transdifferentiate. Advisory Action ¶ 2. As already discussed, however, the '506 Patent does not describe the presently claimed astrocytes. Therefore it is believed that this statement has been rebutted by the remarks set forth herein.

The presently claimed culturing process is advantageously free of the necessity to develop and maintain the homogenous population of CNS stem cells taught in the '506 Patent. Instead, astrocyte cultures may be developed and maintained with ease, and then used to develop other cell types. Since the '506 Patent does not teach or suggest all of the presently claimed limitations, there can be no prima facie case of rejection, and withdrawal of rejections based on the '506 Patent is requested.

CONCLUSIONS AND REQUEST FOR RELIEF

Applicants submit that claims 65-89 are in condition for allowance. Thus, Applicants respectfully request the reversal of the rejections of, and objections to, claims 65-89, and the allowance of the application.

Respectfully submitted,

Curtis B. Herbert, Esq.
Registration No. 45,443

Customer No. 24113
Patterson, Thuente, Skaar & Christensen, P.A.
4800 IDS Center
80 South 8th Street
Minneapolis, Minnesota 55402-2100
Telephone: (612) 349-3008

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APPENDIX A

PENDING CLAIMS

65. An in vitro method to produce a population that includes neurons and/or oligodendrocytes, the method comprising:

(a) preparing an in vitro cell culture consisting essentially of astrocytes derived from a human neural stem cell;

(b) dissociating and plating the in vitro cell culture; and

(c) maintaining the in vitro cell culture in medium essentially free of serum comprising bFGF for at least one day,

to produce a population of cells that include neurons and/or oligodendrocytes.

66. The method of claim 65, further comprising, before (b), maintaining the in vitro cell culture in the presence of bFGF.

67. The method of claim 65, wherein (c) maintaining the in vitro cell culture in medium comprising bFGF, is performed for at least 10 days.

68. The method of claim 65, wherein (c) maintaining the in vitro cell culture in medium comprising bFGF for at least one day further comprises mechanically disrupting cell clusters.

69. The method of claim 65, further comprising, after (c), maintaining the in vitro cell culture in a medium in the absence of bFGF.

70. The method of claim 69 wherein the medium comprises DMEM.

71. The method of claim 69 wherein the medium comprises F12.

72. The method of claim 69 wherein the medium comprises FGF-8.

73. The method of claim 69 wherein the medium comprises a member of the group consisting of retinoic acid, dbcAMP, BDNF, and GDNF.

74. The method of claim 65, wherein the cells are plated onto a substrate that comprises a member of the group consisting of poly L-lysine, polyornithine, and extracellular matrix.

75. The method of claim 65, wherein the concentration of the bFGF is in the range of 0.05 to 1000 ng per ml.

76. The method of claim 65, wherein heparin is present with the bFGF.

77. The method of claim 65, wherein said method is used as a control step to identify other compounds that may exert a similar transdifferentiation effect on the astrocytes.

78. The method of claim 77, further comprising, before (b), maintaining the in vitro cell culture in the presence of bFGF.

79. The method of claim 77, wherein (c) maintaining the in vitro cell culture in medium comprising bFGF, is performed for at least 10 days.

80. The method of claim 77, wherein (c) maintaining the in vitro cell culture in medium comprising bFGF for at least one day further comprises mechanically disrupting cell clusters.

81. The method of claim 77, further comprising, after (c), maintaining the in vitro cell culture in a medium in the absence of bFGF.

82. The method of claim 77 wherein the medium comprises DMEM.

83. The method of claim 77 wherein the medium comprises F12.

84. The method of claim 77 wherein the medium comprises FGF-8.

85. The method of claim 77 wherein the medium comprises a member of the group consisting of retinoic acid, dbcAMP, BDNF, and GDNF.

86. The method of claim 85, wherein the cells are plated onto a substrate that comprises a member of the group consisting of poly L-lysine, polyornithine, and extracellular matrix.

87. The method of claim 77, wherein the concentration of the bFGF is in the range of 0.05 to 1000 ng per ml.

88. The method of claim 77, wherein heparin is present with the bFGF.

89. The method of claim 77 wherein the compound comprises at least one neurotrophin.